hypodermic needle and syringe, remove all of the withdrawable contents from each container if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute the stock solution with solution 1 to the reference concentration of 1 microgram of mitomycin per milliliter (estimated).

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(a) of this chapter, using a solution containing 0.5 milligram of mitomycin per milliliter.

(4) [Reserved]

(5) *Depressor substances.* Proceed as directed in §436.35 of this chapter.

(6) *Moisture.* Proceed as directed in §436.201 of this chapter.

(7) *pH.* Proceed as directed in §436.202 of this chapter using the drug reconstituted as directed in the labeling.

(8) *Identity.* Proceed as directed in §436.310 of this chapter.

[39 FR 19145, May 30, 1974, as amended at 46 FR 60568, Dec. 11, 1981; 50 FR 19920, May 13, 1985]

PART 452—MACROLIDE ANTIBIOTIC DRUGS

Subpart A—Bulk Drugs

Subpart B—Oral Dosage Forms

Subpart C—Injectable Dosage Forms

Subpart D—Ophthalmic Dosage Forms

AUTHORITY: Sec. 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357).

Subpart A—Bulk Drugs

§452.10 Erythromycin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin is the odorless, white to grayish-white or slightly yellow compound of a kind of erythromycin or a mixture of two or more such compounds. It is so purified and dried that:

(i) It contains not less than 850 micrograms of erythromycin per milligram calculated on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 10 percent.

(iv) Its pH is not less than 8.0 or more than 10.5.

(v) Its residue on ignition is not more than 2.0 percent.

(vi) Its heavy metals content is not more than 50 parts per million.

(vii) It gives a positive identity test for erythromycin.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, residue on ignition, heavy metals, pH, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing not less than 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Dilute this solution further with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution containing 1.0 milligram of erythromycin base per milliliter (estimated). Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) [Reserved]

(3) *Moisture.* Proceed as directed in §436.201 of this chapter.

(4) *pH.* Proceed as directed in §436.202 of this chapter, except standardize the pH meter with pH 7.0 and pH 10.0 buffers and prepare the sample as follows: Dissolve 200 milligrams of sample in 5 milliliters of reagent grade methyl alcohol. Add 95 milliliters of water and mix. Record the pH when an equilibrium value has been reached.

(5) *Residue on ignition.* Proceed as directed in §436.207(a) of this chapter.

(6) *Heavy metals.* Proceed as directed in §436.208 of this chapter.

(7) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

(8) *Identity test.* Proceed as directed in §436.211 of this chapter, using the sample preparation method described in paragraph (b)(3) of that section.

[39 FR 19149, May 30, 1974, as amended at 42 FR 38564, July 29, 1977; 43 FR 9801, Mar. 10, 1978; 50 FR 19920, May 13, 1985]

§452.15 Erythromycin estolate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin estolate is the lauryl sulfate salt of the propionyl ester of a kind of erythromycin or a mixture of two or more such salts. It occurs as a white powder. It is soluble in alcohol, methyl alcohol, acetone,

and chloroform, but is practically insoluble in water. It is so purified and dried that:

(i) It contains not less than 600 micrograms of erythromycin per milligram, calculated on an anhydrous basis.

(ii) Its free erythromycin content is not more than 3.0 percent.

(iii) Its moisture content is not more than 4.0 percent.

(iv) Its pH is not less than 4.5 nor more than 7.0.

(v) It gives positive identity tests for erythromycin estolate.

(vi) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, free erythromycin content, moisture, pH, crystallinity, and identity.

(ii) Samples of the batch: A minimum of 10 containers, each containing not less than 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Immediately dilute this solution further with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a concentration of 0.1 milligram of erythromycin per milliliter (estimated). Hydrolyze this solution in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Free erythromycin content.* Proceed as directed in § 436.362 of this chapter.

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous suspension containing 10 milligrams per milliliter.

(5) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(6) *Identity test.* Proceed as directed in § 436.211 of this chapter, preparing the sample as described in paragraph (b)(1) of that section.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, May 13, 1985; 53 FR 1920, Jan. 25, 1988]

§ 452.25 Erythromycin ethylsuccinate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate is the white, odorless, ethylsuccinate ester of erythromycin. It is so purified and dried that:

(i) It contains not less than 765 micrograms of erythromycin per milligram, calculated on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 3.0 percent.

(iv) Its pH is not less than 6.0 and not more than 8.5.

(v) Its residue on ignition is not more than 1.0 percent.

(vi) It gives a positive identity test for erythromycin ethylsuccinate.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 1 milligram of erythromycin base per milliliter (estimated). Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a 1.0 percent suspension in water.

(5) *Residue on ignition.* Proceed as directed in § 436.207(a) of this chapter.

(6) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample prepared as described in paragraph (b)(3) of that section.

(7) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, May 13, 1985]

§ 452.25a Sterile erythromycin ethylsuccinate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate is the white, odorless, ethylsuccinate ester of erythromycin. It is so purified and dried that:

(i) It contains not less than 765 micrograms of erythromycin per milligram, calculated on an anhydrous basis.

(ii) It is sterile.

(iii) [Reserved]

(iv) Its moisture content is not more than 3.0 percent.

(v) Its pH is not less than 6.0 and not more than 8.5.

(vi) Its residue on ignition is not more than 1.0 percent.

(vii) It gives a positive identity test for erythromycin ethylsuccinate.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, moisture, pH, residue on ignition, identity, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 1 milligram of erythromycin base per milliliter (estimated). Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section.

(3) [Reserved]

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using a 1.0 percent suspension in water.

(6) *Residue on ignition.* Proceed as directed in § 436.207(a) of this chapter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(3) of that section.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, May 13, 1985]

§ 452.30a Sterile erythromycin gluceptate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin gluceptate is the white powder of the glucoheptonic acid salt of erythromycin or a mixture of two or more such salts. It is freely soluble in water, alcohol, and methyl alcohol. It is slightly soluble in acetone and chloroform, but is practically insoluble in ether. It is so purified and dried that:

(i) It contains not less than 600 micrograms of erythromycin per milligram, calculated on an anhydrous basis. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain.

(ii) It is sterile.

(iii) [Reserved]

(iv) It is nonpyrogenic.

(v) Its moisture content is not more than 5.0 percent.

(vi) Its pH in an aqueous solution containing 25 milligrams per milliliter is not less than 6.0 nor more than 8.0.

(vii) It gives a positive identity test for erythromycin gluceptate.

(2) [Reserved]

(3) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(4) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing not less than 300 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 12 immediate containers of the batch.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: If the batch is packaged for repacking or for use in manufacturing another drug, dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Dilute this solution further with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution containing 1.0 milligram of erythromycin base per milliliter (estimated). If it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 3 to give a stock solution of convenient concentration. Further dilute the stock solution with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 30 milligrams of erythromycin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using a concentration of 25 milligrams per milliliter.

(7) *Identity*. Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

[39 FR 19149, May 30, 1974, as amended at 46 FR 16685, Mar. 13, 1981; 50 FR 19920, 19921, May 13, 1985]

§ 452.32a Sterile erythromycin lactobionate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Erythromycin lactobionate is the white to off-white powder of the lactobionate salt of erythromycin or a mixture of two or more such salts. It is so purified and dried that:

(i) If the erythromycin lactobionate is not packaged for dispensing, its erythromycin potency is not less than 525 micrograms of erythromycin per milligram on an anhydrous basis. If the erythromycin lactobionate is packaged for dispensing, its erythromycin potency is not less than 525 micrograms of erythromycin per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 5.0 percent.

(v) Its pH is not less than 6.5 and not more than 7.5.

(vi) Its residue on ignition is not more than 2.0 percent.

(vii) Its heavy metals content is not more than 50 parts per million.

(viii) It passes the identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, residue on ignition, heavy metals, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(*1*) For all tests except sterility: A minimum of 12 immediate containers.

(*2*) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 12 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows:

(i) *Product not packaged for dispensing (micrograms of erythromycin per milligram).* Dissolve an accurately weighed sample with sufficient methyl alcohol to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute an aliquot of this solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(ii) *Product packaged for dispensing.* Determine both micrograms of erythromycin per milligram of sample and milligrams of erythromycin per container. Use separate containers for preparation of each sample solution as described in paragraph (b)(1)(ii)(*a*) and (*b*) of this section.

(*a*) *Micrograms of erythromycin per milligram.* Dissolve an accurately weighed sample with sufficient methyl alcohol to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute an aliquot of this solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(*b*) *Milligrams of erythromycin per container.* Reconstitute the sample as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute an aliquot of the solution thus obtained with sterile distilled water to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute an aliquot of this solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 30 milligrams of erythromycin per milliliter.

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using a concentration of 50 milligrams of erythromycin per milliliter.

(6) *Residue on ignition.* Proceed as directed in § 436.207(a) of this chapter.

(7) *Heavy metals.* Proceed as directed in § 436.208 of this chapter.

(8) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(3) of that section.

[51 FR 35215, Oct. 2, 1986, as amended at 55 FR 11584, Mar. 29, 1990]

§ 452.35 Erythromycin stearate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin stearate is the odorless, white or slightly yellow powder of the stearic acid salt of erythromycin. It is practically insoluble in water but is soluble in alcohol, methyl alcohol, chloroform, and ether. It is so purified and dried that:

(i) It contains not less than 550 micrograms of erythromycin per milligram, calculated on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 4.0 percent.

(iv) Its pH is not less than 6.0 and not more than 11.0.

(v) Its residue on ignition is not more than 1.0 percent.

(vi) It gives positive identity tests for erythromycin stearate.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH residue on ignition, identity, and crystallinity.

(ii) Samples required: A minimum of 10 containers, each consisting of 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 1 milligram of erythromycin base per milliliter (estimated). Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a 1 percent slurry of erythromycin stearate in water.

(5) *Residue on ignition.* Proceed as directed in § 436.207(a) of this chapter.

(6) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

(7) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, 19921, May 13, 1985]

§ 452.50 Clarithromycin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Clarithromycin is 6-O-methylerythromycin A. It is so purified and dried that:

(i) Its potency is not less than 960 micrograms of clarithromycin activity per milligram, on an anhydrous basis.

(ii) Its moisture content is not more than 2.0 percent.

(iii) The pH of a 0.2 percent (weight per volume) slurry in aqueous methanol (95:5) is not less than 7.5 and not more than 10.0.

(iv) Its residue on ignition is not more than 0.3 percent.

(v) Its heavy metals content is not more than 20 parts per million.

(vi) Its specific rotation in chloroform containing 10 milligrams of clarithromycin per milliliter at 20 °C is between -89° and -95°, calculated on an anhydrous basis.

(vii) It gives a positive identity test.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for clarithromycin potency, moisture, pH, residue on ignition, heavy metals, specific rotation, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.216 of this chapter, using a constant column temperature of 50 °C, a suitable ultraviolet detection system operating at 210 nanometers, an analytical column 3 to 30 centimeters long packed with a reversed phase packing material such

as octadecyl hydrocarbon bonded silicas (3 to 10 micrometers in diameter), the inlet of this column is connected to a guard column 1 to 5 centimeters in length packed with the same material of 5- to 30-micrometer particle size, a constant flow rate of 0.7 to 1.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. The retention time for clarithromycin is between 5 and 6 minutes and the retention time for 6,11-Di-O-methylerythromycin A (resolution compound) is between 7 and 8 minutes. Mobile phase, system suitability solution, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Mobile phase.* Add 650 milliliters of methanol and 350 milliliters of 0.067 *M* potassium phosphate (monobasic) to a suitable container, mix well, and adjust the pH to 4.0 with phosphoric acid. Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) *Preparation of system suitability solution.* Prepare a methanol solution containing approximately 625 micrograms per milliliter each of clarithromycin and 6,11-Di-O-methylerythromycin A. Quantitatively transfer an aliquot of this solution to a suitable volumetric flask and dilute it to volume with mobile phase to obtain a solution containing approximately 125 micrograms each of clarithromycin and 6,11-Di-O-methylerythromycin A.

(iii) *Preparation of working standard solution.* Dissolve (by shaking or sonication) an accurately weighed portion of the clarithromycin working standard in sufficient methanol to obtain a known solution containing about 625 micrograms of clarithromycin activity per milliliter. Quantitatively transfer an aliquot of this solution to a suitable volumetric flask and dilute to volume with mobile phase and mix to obtain a known solution containing approximately 125 micrograms of clarithromycin activity per milliliter. Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter.

(iv) *Sample solution.* Dissolve (by shaking or sonication) an accurately weighed portion of the sample in sufficient methanol to obtain a solution containing 625 micrograms of clarithromycin activity per milliliter (estimated). Quantitatively transfer an aliquot of this solution to a suitable volumetric flask and dilute to volume with mobile phase and mix to obtain a known solution containing approximately 125 micrograms of clarithromycin activity per milliliter (estimated). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter.

(v) *System suitability requirements*—(A) *Asymmetry factor.* The asymmetry factor (A_S) is satisfactory if it is not less than 0.9 and not more than 1.5 for the clarithromycin peak.

(B) *Efficiency of the column.* The absolute efficiency (h_r) is satisfactory if it is not more than 40.0 for the clarithromycin peak.

(C) *Resolution factor.* The resolution factor (R) between the peak for clarithromycin and the peak for 6,11-Di-O-methylerythromycin A is satisfactory if it is not less than 2.0.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent of 5 replicate injections) is satisfactory if it is not more than 2.0 percent.

(E) *Capacity factor.* Calculate the clarithromycin capacity factor (k') as follows:

$$k' = (t_r/t_0) - 1$$

where:

t_r = Retention time of the clarithromycin peak; and

t_0 = Void volume time.

The capacity factor is satisfactory if it is not less than 1.3 and not more than 4.0. If the system suitability parameters have been met, then proceed as described in § 436.216(b) of this chapter.

(vi) *Calculations.* Calculate the micrograms of clarithromycin per milligram of sample on an anhydrous basis as follows:

$$\text{Micrograms of clarithromycin per milligram} = \frac{A_U \times P_S \times 100}{A_S \times C_U \times (100 - m)}$$

where:

A_U = Area of the clarithromycin peak (at a retention time equal to that observed for the clarithromycin standard) in the chromatogram of the sample;

A_S = Area of the clarithromycin peak in the chromatogram of the clarithromycin working standard;

P_S = Clarithromycin activity in the clarithromycin working standard solution in micrograms per milliliter;

C_U = Milligrams of sample per milliliter of sample solution; and

m = Percent moisture content of the sample.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter, using the sample preparation described in paragraph (d)(1) of that section and the titration procedure described in paragraph (e)(3) of that section, except that instead of adding 20 milliliters of solvent A before starting the titration, add a sufficient volume of solvent C to cover the electrodes in the dry titrating vessel.

(3) *pH.* Proceed as directed in §436.202 of this chapter, except standardize the pH meter with pH 7.0 and pH 10.0 buffers and prepare the sample as follows: Transfer 200 milligrams of the sample to a 150-milliliter beaker. Add 5 milliliters of methanol and then 95 milliliters of distilled water. Place the pH electrodes in the slurry and stir at the slowest speed possible to ensure mixing but no vortex. After 10 minutes, while still stirring, determine the pH.

(4) *Residue on ignition.* Proceed as directed in §436.207(a) of this chapter.

(5) *Heavy metals.* Proceed as directed in §436.208 of this chapter.

(6) *Specific rotation.* Dilute an accurately weighed sample with sufficient chloroform to give a concentration of approximately 10 milligrams of clarithromycin per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube, maintaining the solution at 20 °C, and calculate the specific rotation on an anhydrous basis.

(7) *Identity.* Proceed as directed in §436.211 of this chapter, preparing the sample as follows: Prepare a 5-percent solution of the sample in chloroform and use 0.1 millimeter matched absorption cells.

(8) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[58 FR 26653, May 4, 1993]

§452.60 Azithromycin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Azithromycin is the dihydrate form of (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-O-methyl-α-*L*-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. It is so purified and dried that:

(i) Its potency is not less than 945 micrograms and not more than 1,030 micrograms of azithromycin activity per milligram, on the anhydrous basis.

(ii) Its moisture content is not less than 4.0 percent and not more than 5.0 percent.

(iii) The pH of an aqueous methanol (1:1) solution containing 2 milligrams per milliliter is not less than 9 and not more than 11.

(iv) Its residue on ignition is not more than 0.3 percent.

(v) Its heavy metals content is not more than 25 parts per million.

(vi) The specific rotation in absolute ethanol containing 20 milligrams of azithromycin per milliliter at 20 °C is between -45° to -49°, calculated on an anhydrous basis.

(vii) It is crystalline.

(viii) It gives a positive identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for azithromycin potency, moisture, pH, residue on ignition, heavy metals, specific rotation, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.216 of

this chapter, using ambient temperature, an amperometric electrochemical detection system with dual glassy carbon electrodes operated in the oxidative screen mode with electrode 1 set at +0.70 volt±0.05 volt and electrode 2 at +0.82 volt±0.05 volt. (The ±0.05-volt variance allows for optimization of the background current to 70 to 100 nanoamperes.) Detection of azithromycin occurs at electrode 2 where the voltage is sufficiently high to oxidize the amine functional groups on the molecules. Use a 15-centimeters by 4.6-millimeters (inside diameter) column packed with alumina-based polybutadiene 5 micrometer spherical particles with 80-angstrom pore size (e.g., ES Industries γRP1/p). The inlet of this column is connected to a guard column 5 centimeters by 4.6 millimeters (inside diameter) packed with the same material. The flow rate is 1.5 milliliters per minute. Use a fixed volume loop injector or equivalent device to inject a volume of 50 microliters into the system. The retention time for azithromycin is between 10 and 13 minutes. Mobile phase, working standard, sample, and resolution solutions, system suitability requirements, and calculations are as follows:

(i) *Mobile phase.* Dissolve 5.8 grams of potassium phosphate monobasic in 2,130 milliliters of ultrapure deionized or high-performance liquid chromatographic-grade water. Add 870 milliliters of acetonitrile and mix. The mobile phase is 0.02 *M* potassium phosphate monobasic: acetonitrile (71:29). Adjust the pH of the mobile phase to pH 11.0±0.1 with 10 *M* potassium hydroxide (about 6 milliliters). Filter the mobile phase through a suitable filter capable of removing particulate matter 0.5 micron in diameter and degas it just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard solution.* Accurately weigh approximately 16.5 milligrams of the azithromycin working standard into a 100-milliliter volumetric flask. Dissolve the material, aided by brief sonication, in 10 milliliters of acetonitrile and dilute to volume with acetonitrile. Pipet 2.0 milliliters of this solution into a 100-milliliter volumetric flask and dilute to volume with mobile phase. This solution contains approximately 0.003 milligram per milliliter of azithromycin.

(iii) *Sample solution.* Accurately weigh approximately 16.5 milligrams of sample into a 100-milliliter volumetric flask. Dissolve the sample, aided by brief sonication, in 10 milliliters of acetonitrile and dilute to volume with acetonitrile. Pipet 2.0 milliliters of this solution into a 100-milliliter volumetric flask and dilute to volume with mobile phase.

(iv) *Resolution test solution.* Weigh approximately 16.5 milligrams each of azithromycin working standard and azaerythromycin A reference standard into a 100-milliliter volumetric flask. Dissolve the materials aided by brief sonication in 10 milliliters of acetonitrile and dilute to volume with acetonitrile. Pipet 2.0 milliliters of this solution into a 100-milliliter volumetric flask and dilute to volume with mobile phase.

(v) *System suitability requirements.* Using the resolution test solution, determine the:

(A) *Asymmetry factor.* The asymmetry factor (A_S) is satisfactory if it is not less than 0.9 and not more than 1.5 for the azithromycin peak.

(B) *Efficiency of the column.* The absolute efficiency (h_r) is satisfactory if it is not more than 40.0 for the azithromycin peak.

(C) *Resolution factor.* The resolution factor (R) between the peak from azithromycin and the peak for azaerythromycin A is satisfactory if it is not less than 2.5.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent of 5 replicate injections) is satisfactory if it is not more than 2.0 percent. If the system suitability parameters have been met, then proceed as described in § 436.216(b) of this chapter.

(vi) *Calculations.* Calculate the micrograms of azithromycin per milligram of sample on an anhydrous basis as follows:

$$\text{Micrograms of azithromycin per milligram} = \frac{A_U \times P_S \times 100}{A_S \times C_U \times (100 - m)}$$

where:

A_U = Area of the azithromcin peak (at a retention time equal to that observed for the azithromycin standard) in the chromatogram of the sample;

A_S = Area of the azithromcin peak in the chromatogram of the azithromycin working standard;

P_S Azithromycin activity in the azithromycin working standard solution in micrograms per milliliter;

C_U = Milligrams of sample per milliliter of sample solution; and

m = Percent moisture content of the sample.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous methanol (1:1) solution containing 2 milligrams per milliliter, prepared by diluting a methanol solution containing 4 milligrams of azithromycin dihydrate 1:1 with distilled water.

(4) *Residue on ignition.* Proceed as directed in § 436.207(b) of this chapter, except use a temperature of 800 °C instead of a temperature range of 500 to 600 °C.

(5) *Heavy metals.* Proceed as directed in § 436.208 of this chapter.

(6) *Specific rotation.* Dissolve an accurately weighed sample with sufficient absolute ethanol to give a concentration of approximately 20 milligrams per milliliter. Proceed as directed in § 436.210 of this chapter, except dilute and maintain the test solution at 20 °C instead of 25 °C. Use a 1.0-decimeter polarimeter tube and calculate the specific rotation on an anhydrous basis.

(7) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(8) *Identity.* Proceed as directed in § 436.211 of this chapter, using a 0.5 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

[58 FR 26657, May 4, 1993]

§ 452.75 Troleandomycin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Troleandomycin is the triacetyl ester of oleandomycin base or a mixture of two or more such esters. It is a white powder. It is so purified that:

(i) Its potency is not less than 750 micrograms of troleandomycin per milligram.

(ii) [Reserved]

(iii) Its loss on drying is not more than 1.0 percent.

(iv) Its pH in an aqueous alcohol solution containing 100 milligrams of troleandomycin per milliliter is not less than 7.0 and not more than 8.5.

(v) Its residue on ignition is not more than 0.1 percent.

(vi) It gives a positive identity test for oleandomycin.

(vii) Its R_f value by paper chromatography is approximately 0.85. If more than one spot appears on the paper chromatogram, determine its acetyl value, which is not less than 15.3 percent and not more than 16.0 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, loss on drying, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(ii) Samples of the batch: 10 packages, nine containing approximately equal portions of not less than 500 milligrams, and one containing not less than 2.0 grams.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the microbiological turbidimetric assay shall be conclusive.

(i) *Chemical method*—(*a*) *Reagents and equipment.* (*1*) Methyl orange reagent: Shake 0.5*M* boric acid solution for 12 hours (to ensure saturation) with an excess of methyl orange indicator. An alternative method is to heat the mixture to about 50° C. and shake for about an hour. Then allow to cool. Filter the saturated dye solution and wash three times with chloroform. Store the dye solution over chloroform.

(*2*) Acid-alcohol solution: Add 2 milliliters of concentrated sulfuric acid to

98 milliliters of absolute methyl alcohol.

(*3*) Glycerin: Reagent grade.

(*4*) Chloroform.

(*5*) Glacial acetic acid.

(*6*) Centrifuge tubes: 40 milliliters, glass-stoppered.

(*b*) *Procedure.* Using the troleandomycin working standard which has been dried for 3 hours at 60° C. and a pressure of 5 millimeters or less, prepare a standard solution in chloroform containing 50.0 milligrams of oleandomycin base in 200 milliliters. Transfer 10.0 milliliters of the solution to a 100-milliliter volumetric flask and dilute to volume with chloroform. Transfer 2.0, 4.0, 6.0, and 8.0 milliliters of this solution to glass-stoppered centrifuge tubes (40-milliliter size) and dilute to a total volume of 20.0 milliliters each with chloroform. To the 20 milliliters of the solution present in each 40-milliliter size centrifuge tube, add 0.2 milliliter of glacial acetic acid, 0.2 milliliter of glycerin, and 0.4 milliliter of methyl orange reagent. Shake for 5 minutes and centrifuge for 3 minutes. Immediately transfer to another tube a 10.0-milliliter aliquot from the chloroform (lower) layer. Care must be exercised to see that no portion of the dye-glycerin phase is included with the chloroform aliquot. Add 1.0 milliliter of acid-alcohol solution to this chloroform aliquot, mix well, and read the absorbancy at 535 nanometers, using a 1-centimeter cell and a suitable photometer and using chloroform, similarly treated, as a blank. Prepare a standard curve, plotting the absorbance values of the standard solution against the concentration expressed in micrograms of oleandomycin base per aliquot. Accurately weigh the sample to be tested to give 50 milligrams (estimated) of oleandomycin base. Dissolve in chloroform and make to 200 milliliters with chloroform. Transfer 10.0 milliliters to a 100-milliliter volumetric flask and make to volume with chloroform. Transfer 5.0 milliliters to a glass-stoppered centrifuge tube and proceed as above. Determine the potency of the sample from the standard curve.

(ii) *Microbiological turbidimetric assay.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 80 percent isopropyl alcohol solution (solution 15) to obtain a stock solution containing 1,000 micrograms per milliliter. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 25 micrograms of troleandomycin per milliliter (estimated).

(2) [Reserved]

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a saturated solution prepared by adding 100 milligrams of troleandomycin per milliliter of water-ethyl alcohol (1:1) diluent.

(5) *Residue on ignition.* Proceed as directed in § 436.207(a) of this chapter, except use a silica crucible.

(6) *Identity.* Dissolve about 10 milligrams in 5 milliliters of hydrochloric acid and heat the solution in a boiling water bath; a greenish yellow color is produced.

(7) *Rf value*—(i) *Apparatus and reagents.* (*a*) Chromatographic chamber (cylinder, glass-stoppered museum jar, 11.5 inches x 3.5 inches).

(*b*) Chromatographic paper (8 inches x 8 inches, Whatman No. 1).

(*c*) 0.1*N* hydrochloric acid.

(*d*) Resolving solvent: Butyl acetate, benzene, nitromethane, pyridine (5:5:5:1 by volume).

(*e*) Spray developing reagent: Place 1.0 milliliter of 10 percent platinic chloride solution and 25.0 milliliters of 4 percent potassium iodide solution in a 250-milliliter volumetric flask. Fill to mark with distilled water and mix well.

(ii) *Procedure.* Dissolve the sample in chloroform to give a solution containing 10 to 20 milligrams of oleandomycin base equivalent per milliliter. Prepare a sheet of chromatographic paper by drawing a line of origin parallel to and 1 inch from the edge of the paper. Wet the paper thoroughly with the 0.1*N* hydrochloric acid and blot it firmly between sheets of absorbent paper. Starting 2 inches in from the edge and at 1-inch intervals, apply 3 to 5 microliters of the sample solutions to the starting line. Allow a few minutes for the paper to dry partially. While it is still damp,

form a cylinder by bringing the outer edges together, allowing about 1-inch overlap, and secure with a paper clip. Stand the paper in the chromatographic chamber, which has been filled to a depth of one-half of an inch with the resolving solvent. After the solvent front rises to a height of 4 to 5 inches above the origin, remove the paper from the tank and hang it up to air dry. Spray the dried paper with the developing reagent. Hang the paper in a 100° C. oven for 3 minutes. A purple spot becomes visible for troleandomycin at an R_f value of about 0.85. The approximate R_f values for diacetyloleandomycin, monoacetyloleandomycin, and oleandomycin are, respectively, 0.72, 0.27, and 0.13.

(8) *Acetyl determination*—(i) *Apparatus and reagents.* (*a*) One 3-necked Pyrex flask of approximately 45 milliliters capacity, pear-shaped with T-joints, agar inlet tube, glass-stoppered funnel, glass condenser, and bubble counter.

(*b*) 50-milliliter Pyrex Erlenmeyer flask.

(*c*) 10-milliliter buret, calibrated to 0.02 milliliter.

(*d*) Anhydrous methyl alcohol, reagent grade.

(*e*) 2*N* sodium hydroxide solution.

(*f*) Sulfuric acid solution prepared by adding 100 milliliters of concentrated H_2SO_4 to 200 milliliters of water.

(*g*) 1*N* barium chloride solution.

(*h*) Phenolphthalein solution (1 percent in ethyl alcohol).

(*i*) Water-pumped nitrogen.

(*j*) NaOH solution 0.015*N*.

(ii) *Procedure.* Weigh accurately (to 0.01 milligram) approximately 30 milligrams of the sample into the three-necked acetyl flask. Add 2.0 milliliters of methyl alcohol to dissolve the sample; then add slowly, with gentle swirling, 1.0 milliliter of NaOH solution. Connect the gas inlet tube with bubble counter attached and adjust nitrogen flow to about two bubbles a second. Put glass-stoppered funnel in centerneck of acetyl flask and put about 5 milliliters of H_2O in the funnel. Add a boiling chip to the solution and attach condenser in the refluxing position with water cooling. Adjust burner flame under acetyl flask to reflux solution gently. Reflux for 30 minutes. Cool assembly slightly; then rinse down condenser (still in reflux position) with a few milliliters of H_2O. Reassemble condenser to the distillation position and add water through the funnel to make a total of approximately 5 milliliters of H_2O added to acetyl flask. Adjust burner flame so that about 5 milliliters of H_2O and methyl alcohol is distilled over in approximately 10 minutes. Discard this distillate. Cool acetyl flask slightly. Acidify solution in flask by adding 1 milliliter of the sulfuric acid solution through the funnel. Adjust burner flame and distill over approximately 20 milliliters of distillate into an Erlenmeyer flask in about 20 minutes, adding water through the funnel as necessary. It is important to keep the liquid volume in the acetyl flask around 2 to 3 milliliters in order to obtain a quantitative recovery of the acetic acid. Collect a second fraction of distillate, about 10 milliliters in volume. As the second fraction is distilling, process the first fraction. Heat the first fraction and boil gently about 20 seconds. Add a few drops of $BaCl_2$ solution to check if any sulfate was distilled over. If the sulfate is present, discard and repeat the whole determination. If the sulfate is absent, immediately titrate the solution with the 0.015*N* NaOH solution to a faint-pink endpoint, using one drop of phenolphthalein solution as the indicator. Repeat the above procedure with the second fraction. If the second fraction requires less than 0.10 milliliter of the 0.015*N* NaOH solution and all the acetic acid has been distilled over, the determination is completed. If greater than this, collect a third fraction of approximately 10 milliliters and titrate this as before. Total volumes of NaOH used and calculate results as follows:

(Milliliters of NaOH×*N* NaOH×0.043×100)/(Weight sample in grams)=Percent acetyl.

(9) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 48 FR 3960, Jan. 28, 1983; 50 FR 19920, 19921, May 13, 1985]

Subpart B—Oral Dosage Forms

§452.110 Erythromycin oral dosage forms.

§452.110a Erythromycin tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin tablets are erythromycin with suitable and harmless buffer substances, diluents, binders, lubricants, colorings, flavorings, and suitable preservatives. The potency of each tablet is 250 milligrams or 500 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Tablets shall disintegrate within 1 hour. The loss on drying is not more than 5.0 percent. The erythromycin used in making the batch conforms to the standards prescribed by §452.10(a)(1), except heavy metals.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, pH, moisture, residue on ignition, crystallinity, and identity.

(*b*) The batch for potency, disintegration time, and loss on drying.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing 500 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of tablets in a high-speed glass blender for 2 to 3 minutes with 200 milliliters of methyl alcohol. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

(3) *Disintegration time.* Proceed as directed in §436.212 of this chapter, using the procedure described in paragraph (e)(2) of that section.

[39 FR 19149, May 30, 1974, as amended at 42 FR 59068, Nov. 15, 1977; 50 FR 19921, May 13, 1985]

§452.110b Erythromycin enteric-coated tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromyin enteric-coated tablets are enteric-coated tablets composed of erythromycin, suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains 100, 250, 333, or 500 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. The tablets shall disintegrate within 2 hours. The moisture content is not more than 6 percent. The erythromycin base used in making the batch conforms to the standards of §452.10(a)(1) (i), (iii), (iv), (v), (vii), and (viii).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, moisture, pH, residue on ignition, crystallinity, and identity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing 500 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of tablets in a high-speed glass blender for 2 to 3 minutes with 200 milliliters of methyl alcohol. Add

300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter, using the procedure described in paragraph (e)(3) of that section.

[39 FR 14149, May 30, 1974, as amended at 44 FR 30332, May 25, 1979; 44 FR 48190, Aug. 17, 1979; 46 FR 44442, Sept. 4, 1981; 47 FR 15326, Apr. 9, 1982; 50 FR 19921, May 13, 1985]

§ 452.110c Erythromycin capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin capsules are capsules containing enteric-coated erythromycin pellets, suitable and harmless buffer substances, diluents, binders, lubricants, and colorings. Each capsule contains either 125 milligrams or 250 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. The moisture content is not more than 7.5 percent. It passes the acid resistance/dissolution test. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1), except heavy metals.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency, moisture, and acid resistance/dissolution.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 100 capsules.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing 200 milliliters of methyl alcohol. Blend for 2 to 3 minutes. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Further dilute an aliquot with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the sample preparation method described in paragraph (d)(1) of that section.

(3) *Acid resistance/dissolution.* Proceed as directed in § 436.542 of this chapter. The quantity Q (the amount of erythromycin dissolved) is 85 percent at 45 minutes.

[46 FR 16678, Mar. 13, 1981; 46 FR 22359, Apr. 17, 1981, as amended at 50 FR 19921, May 13, 1985; 50 FR 36992, Sept. 11, 1985; 50 FR 47214, Nov. 15, 1985]

§ 452.110d Erythromycin particles in tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin particles in tablets are tablets containing erythromycin acid-resistant coated particles, suitable and harmless diluents, binders, lubricants, and colorings. Each tablet contains 333 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. The loss on drying is not more than 5.0 percent. It passes the dissolution test and the acid resistance test. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1), except heavy metals.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, safety, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency, loss on drying, dissolution, and acid resistance.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) The erythromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 100 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing 200 milliliters of methyl alcohol. Blend for 2 to 3 minutes. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Further dilute an aliquot with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

(3) *Dissolution.* Proceed as directed in §436.215 of this chapter. The quantity *Q* (the amount of erythromycin dissolved) is 75 percent at 45 minutes.

(4) *Acid resistance.* Proceed as directed in §436.545 of this chapter. The quantity of erythromycin dissolved is not more than 25 percent at 60 minutes.

[51 FR 37723, Oct. 24, 1986, as amended at 55 FR 11584, Mar. 29, 1990]

§452.115 Erythromycin estolate oral dosage forms.

§452.115a Erythromycin estolate tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin estolate tablets are composed of erythromycin estolate with one or more suitable and harmless diluents, binders, lubricants, and colorings. Each tablet contains erythromycin estolate equivalent to 500 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. The moisture content is not more than 5 percent. The tablets shall disintegrate within 30 minutes. The erythromycin estolate used conforms to the standards prescribed by §452.15(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin estolate used in making the batch for potency, moisture, pH, identity, and crystallinity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) The erythromycin estolate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch. A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tables into a high-speed glass blender jar with 200 milliliters of methyl alcohol. Blend for 3 to 5 minutes. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 3 to 5 minutes. Hydrolyze a portion of this solution in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in §436.212 of this chapter, using the procedure described in paragraph (e)(1) of that section.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§452.115b Erythromycin estolate capsules.

(a) *Requirements for certification*—(1) *Standards of identity, quality, and purity.* Erythromycin estolate capsules are capsules containing erythromycin

estolate with suitable and harmless buffer substances and diluents enclosed in a gelatin capsule. The erythromycin estolate content of each capsule is equivalent to either 250 milligrams of erythromycin or 125 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. The moisture content is not more than 5 percent. The erythromycin estolate used conforms to the standards prescribed therefor by § 452.15(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain;

(i) Results of tests and assays on:

(*a*) The erythromycin estolate used in making the batch for potency, pH, moisture, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The erythromycin estolate used in making the batch: 10 packages, each containing not less than 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Test and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of capsules in a high-speed glass blender with 200 milliliters of methyl alcohol for 2 to 3 minutes. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Hydrolyze a portion of this solution in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 452.115c Erythromycin estolate oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin estolate oral suspension is erythromycin estolate with suitable and harmless buffer substances, dispersing agents, diluents, coloring, and flavorings. Each milliliter contains erythromycin estolate equivalent to 25, 50, or 100 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. Its pH is not less than 3.5 and not more than 6.5. The erythromycin estolate used conforms to the standards prescribed by § 452.15(a)(1).

(2) *Labeling.* In addition to conforming with the requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the statement ''Refrigerate'' or ''Keep under refrigeration''.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin estolate used in making the batch for potency, moisture, pH, crystallinity, and identity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The erythromycin estolate used in making the batch: 10 containers, each having not less than 300 milligrams.

(*b*) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Remove an accurately measured representative volume of the suspension and dilute with sufficient methyl alcohol to give a concentration of 2.5 milligrams per milliliter (estimated). Dilute the entire mixture with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Hydrolyze in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours.

Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *pH.* Proceed as directed in §436.202 of this chapter, using the drug as it is prepared for dispensing.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§452.115d Erythromycin estolate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin estolate for oral suspension is a dry mixture of erythromycin estolate with suitable and harmless buffer substances, dispersing agents, diluents, colorings, and flavorings. The erythromycin estolate content is 25 milligrams of erythromycin per milliliter of the reconstituted suspension. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. When reconstituted as directed in its labeling, its pH is not less than 5.0 and not more than 7.0. Its moisture content is not more than 2.0 percent. The erythromycin estolate used conforms to the standards of §452.15(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin estolate used in making the batch for potency, moisture, pH, crystallinity, and identity.

(*b*) The batch: Potency, moisture, and pH.

(ii) Samples required:

(*a*) The erythromycin estolate used in making the batch: 10 immediate containers, each consisting of 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Withdraw an accurately measured representative volume of the reconstituted suspension and add sufficient methyl alcohol to give a concentration of 2.5 milligrams of erythromycin base per milliliter (estimated). Dilute this entire mixture with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Hydrolyze in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in §436.201 of this chapter, using the dry powder.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in its labeling.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§452.115e Erythromycin estolate for pediatric drops.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin estolate for pediatric drops is a dry mixture of erythromycin estolate with suitable and harmless dispersing agents, buffer substances, diluents, colorings, and flavorings. When reconstituted as directed in the labeling, each milliliter contains the equivalent of 100 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. Its moisture content is not more than 2.0 percent. Its pH is not less than 5.0 nor more than 5.5. The erythromycin estolate used conforms to the standards prescribed by §452.15(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin estolate used in making the batch for potency, pH, moisture, crystallinity, and identity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The erythromycin estolate used in making the batch: 10 packages, each containing not less than 300 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Withdraw an accurately measured representative volume of the reconstituted suspension and add sufficient methyl alcohol to give a concentration of 2.5 milligrams of erythromycin base per milliliter (estimated). Dilute this entire mixture with sufficient 0.1*M* potassium phosphate buffer, pH 8 (solution 3), to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Hydrolyze in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202(b) of this chapter, using the suspension prepared as directed in the labeling.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 452.115f Erythromycin estolate chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Erythromycin estolate chewable tablets are tablets composed of erythromycin estolate and suitable and harmless diluents, binders, buffers, colorings, and flavorings. Each tablet contains erythromycin estolate equivalent to either 125 or 250 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. The moisture content is not more than 4 percent. The erythromycin estolate used in making the batch conforms to the standards prescribed by § 452.15(a)(1).

(2) *Labeling.* It shall be labeled in accordance with § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin estolate used in making the batch for potency, moisture, pH, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The erythromycin estolate used in making the batch: 10 packages, each consisting of not less than 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of tablets in a high-speed glass blender for 2 to 3 minutes in 200 milliliters of methyl alcohol. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Hydrolyze this solution in a 60° C. constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 452.115g Erythromycin estolate and sulfisoxazole acetyl oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Erythromycin estolate and sulfisoxazole acetyl oral suspension is erythromycin estolate and sulfisoxazole acetyl with suitable and harmless buffer substances, preservatives, solvents, stabilizers, emulsifiers, dispersing agents, colorings, and flavorings. Each milliliter contains erythromycin estolate equivalent to 25 milligrams of erythromycin and 120 milligrams of sulfisoxazole. Its erythromycin content is satisfactory if it is

not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Its sulfisoxazole acetyl content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of sulfisoxazole that it is represented to contain. Its pH is not less than 3.5 and not more than 6.5. The erythromycin estolate used conforms to the standards prescribed by §452.15(a)(1). The sulfisoxazole acetyl used conforms to the standards prescribed by the U.S.P. XXII.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The erythromycin estolate used in making the batch for potency, moisture, pH, crystallinity, and identity.

(B) The sulfisoxazole acetyl used in making the batch for all U.S.P. XXII specifications.

(C) The batch for erythromycin content, sulfisoxazole content, and pH.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The erythromycin estolate used in making the batch: 10 packages, each containing not less than 500 milligrams.

(B) The batch: a minimum of 15 immediate containers.

(b) *Tests and methods of assay*—(1) *Erythromycin content.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Remove an accurately measured representative volume of the suspension and dilute with sufficient methyl alcohol to give a concentration of 2.5 milligrams per milliliter (estimated). Dilute the entire mixture with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Hydrolyze in a 60 °C constant temperature water bath for 2 hours or at room temperature for 16 to 18 hours. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sulfisoxazole content.* Proceed as directed in §436.328 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug as it is prepared for dispensing.

[55 FR 280, Jan. 4, 1990]

§452.125 Erythromycin ethylsuccinate oral dosage forms.

§452.125a Erythromycin ethylsuccinate chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate chewable tablets are composed of erythromycin ethylsuccinate and suitable and harmless diluents, binders, buffers, colorings, and flavorings. Each tablet contains erythromycin ethylsuccinate equivalent to 200 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. The moisture content is not more than 5 percent. The erythromycin ethylsuccinate used conforms to the standards prescribed by §452.25(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''erythromycin ethylsuccinate tablets''.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin ethylsuccinate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The erythromycin ethylsuccinate used in making the batch: 10 packages, each consisting of 500 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of tablets in a high-speed glass blender for 2 to 3 minutes with

200 milliliters of methyl alcohol. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 2 to 3 minutes. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 19149, May 30, 1974, as amended at 41 FR 51596, Nov. 23, 1976; 42 FR 29858, June 10, 1977; 50 FR 19921, May 13, 1985]

§ 452.125b Erythromycin ethylsuccinate oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate oral suspension is erythromycin ethylsuccinate with suitable and harmless buffer substances, dispersing agents, diluents, colorings, flavorings, and preservatives. Each milliliter contains erythromycin ethylsuccinate equivalent to 40 or 80 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Its pH is not less than 6.5 and not more than 8.5. The erythromycin ethylsuccinate used conforms to the standards prescribed by § 452.25(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin ethylsuccinate used in making the batch for potency, moisture, pH, identity, residue on ignition, and crystallinity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The erythromycin ethylsuccinate used in making the batch: 10 containers each consisting of 500 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place an accurately measured representative volume of the suspension into a high-speed glass blender jar and add sufficient methyl alcohol to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Blend for 3 to 5 minutes. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted drug.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 452.125c Erythromycin ethylsuccinate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate for oral suspension is a dry mixture of erythromycin ethylsuccinate with suitable and harmless buffer substances, dispersing agents, diluents, colorings, and flavorings. It contains the equivalent of 40 milligrams or 80 milligrams of erythromycin per milliliter of the reconstituted suspension. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Its loss on drying is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 7.0 nor more than 9.0. The crystalline erythromycin ethylsuccinate used conforms to the standards prescribed by § 452.25(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin ethylsuccinate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch, for potency, pH, and loss on drying.

(ii) Samples required:

(*a*) The erythromycin ethylsuccinate used in making the batch: 10 containers each consisting of approximately 500 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Place an accurately measured representative portion of the sample into a high-speed glass blender jar containing sufficient methyl alcohol to give a final volume of 200 milliliters. Blend for 3 to 5 minutes. Further dilute an aliquot with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension prepared as directed in the labeling. If the suspension contains 80 milligrams per milliliter, equilibrium usually is reached in approximately 15 minutes.

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 47 FR 21240, May 18, 1982; 50 FR 19921, May 13, 1985]

§ 452.125d Erythromycin ethylsuccinate tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate tablets are composed of erythromycin ethylsuccinate and suitable and harmless diluents, binders, buffers, and colorings. Each tablet contains erythromycin ethylsuccinate equivalent to 400 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. The loss on drying is not more than 4.0 percent. The tablets shall disintegrate within 40 minutes. The erythromycin ethylsuccinate used conforms to the standards prescribed by § 452.25(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin ethylsuccinate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency, loss on drying, and disintegration time.

(ii) Samples required:

(*a*) The erythromycin ethylsuccinate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*— (1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient methyl alcohol to yield a concentration of 5 milligrams of erythromycin activity or less per milliliter when blended. Blend for 3 to 5 minutes. Further dilute an aliquot of this solution with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

(3) *Disintegration time*—(i) *If the tablet is uncoated.* Proceed as directed in § 436.212 of this chapter, using the procedure described in paragraph (e)(1) of that section.

(ii) *If the tablet is plain-coated.* Proceed as directed in § 436.212 of this chapter, using the procedure described in paragraph (e)(2) of that section.

[41 FR 51596, Nov. 23, 1976, as amended at 50 FR 19921, May 13, 1985; 55 FR 14091, Apr. 16, 1990]

§ 452.125e Erythromycin ethylsuccinate-sulfisoxazole acetyl for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate-sulfisoxazole acetyl for oral suspension is a dry mixture of erythromycin ethylsuccinate and sulfisoxazole acetyl with suitable and harmless flavorings, buffers, surfactants, colorings, and suspending

agents. When reconstituted as directed in the labeling, each milliliter will contain erythromycin ethylsuccinate equivalent to 40 milligrams of erythromycin and sulfisoxazole acetyl equivalent to 120 milligrams of sulfisoxazole. Its erythromycin ethylsuccinate content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Its sulfisoxazole acetyl content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of sulfisoxazole that it is represented to contain. Its loss on drying is not more than 1.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.0. The erythromycin ethylsuccinate used conforms to the standards prescribed by § 452.25(a)(1). The sulfisoxazole acetyl used conforms to the standards prescribed by the U.S.P.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin ethylsuccinate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The sulfisoxazole acetyl used in making the batch for all U.S.P. specifications.

(*c*) The batch for erythromycin content, sulfisoxazole content, loss on drying, and pH.

(ii) Samples required:

(*a*) The erythromycin ethylsuccinate used in making the batch: 10 packages each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 10 immediate containers.

(b) *Tests and methods of assay*—(1) *Erythromycin content.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Allow to stand for 1 hour. Shake gently and transfer 5 milliliters of the well-shaken suspension into a high-speed glass blender jar containing 195 milliliters of methyl alcohol. Blend for 3 to 5 minutes. Further dilute an aliquot with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sulfisoxazole acetyl content.* Proceed as directed in § 436.328 of this chapter.

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension reconstituted as directed in the labeling.

[46 FR 2990, Jan. 13, 1981, as amended at 50 FR 19921, May 13, 1985]

§ 452.135 Erythromycin stearate oral dosage forms.

§ 452.135a Erythromycin stearate tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin stearate tablets are tablets composed of erythromycin stearate with suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains erythromycin stearate equivalent to 75, 100, 125, 250, or 500 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Tablets shall disintegrate within 1½ hours. The loss on drying is not more than 5.0 percent. The erythromycin stearate used in making the tablets conforms to the standards prescribed by § 452.35(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin stearate used in making the batch for potency, pH, moisture, residue on ignition, crystallinity, and identity.

(*b*) The batch for potency, loss on drying, and disintegration time.

(ii) Samples required:

(*a*) The erythromycin stearate used in making the batch: 10 containers, each consisting of not less than 500 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of tablets in a high-speed glass blender with 200 milliliters of methyl alcohol for 3 to 5 minutes. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 3 to 5 minutes. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter, using the procedure described in paragraph (e)(2) of that section.

[39 FR 19149, May 30, 1974, as amended at 42 FR 59068, Nov. 15, 1977; 50 FR 19921, May 13, 1985]

§ 452.135b Erythromycin stearate oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Erythromycin stearate oral suspension is erythromycin stearate with suitable and harmless buffer substances, dispersing agents, diluents, colorings, and flavorings. It contains the equivalent of 25 milligrams of erythromycin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Its pH is not less than 7.0 and not more than 8.5. The erythromycin stearate used conforms to the standards prescribed by § 452.35(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin stearate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The erythromycin stearate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place an accurately measured representative volume of the suspension into a high-speed glass blender jar. Add sufficient methyl alcohol to the jar to give a concentration of 1.25 milligrams of erythromycin base per milliliter (estimated). Blend for 2 to 3 minutes. Add sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a concentration of 0.5 milligrams of erythromycin base per milliliter (estimated) and blend again for 2 to 3 minutes. Further dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted suspension.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 452.135c Erythromycin stearate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Erythromycin stearate for oral suspension is a dry mixture of erythromycin stearate with suitable and harmless buffer substances, dispersing agents, diluents, colorings, and flavorings. It contains the equivalent of 25 or 50 milligrams of erythromycin per milliliter of the reconstituted suspension. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. Its moisture content is not more than 2 percent. When reconstituted as directed in the labeling, its pH is not less than 6.0 and not more than 9.0. The erythromycin stearate used conforms to the standards prescribed by § 452.35(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin stearate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The erythromycin stearate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Place an accurately measured representative portion of the suspension into a high-speed glass blender jar with sufficient methyl alcohol to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Blend for 3 to 5 minutes. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension obtained when the drug is reconstituted as directed in the labeling.

[40 FR 49083, Oct. 21, 1975, as amended at 41 FR 24884, June 21, 1976; 50 FR 19921, May 13, 1985]

§ 452.150 Clarithromycin tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Clarithromycin tablets are composed of clarithromycin and one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. Each tablet contains 250 milligrams or 500 milligrams of clarithromycin activity. Its clarithromycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of clarithromycin that it is represented to contain. The loss on drying is not more than 6.0 percent. It passes the dissolution test. It passes the identity test. The clarithromycin used conforms to the standards prescribed by § 452.50(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The clarithromycin used in making the batch for potency, moisture, pH, residue on ignition, heavy metals, specific rotation, identity, and crystallinity.

(B) The batch for content, loss on drying, dissolution, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The clarithromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 100 tablets.

(b) *Tests and methods of assay*—(1) *Clarithromycin content.* Proceed as directed in § 452.50(b)(1), preparing the sample solution and calculating the clarithromycin content as follows:

(i) *Preparation of sample solution.* Grind and composite five whole tablets in a glass mortar and pestle and quantitatively transfer the powder to a 500-milliliter volumetric flask with 50 milliliters of distilled water and shake mechanically until the tablets are well dispersed (approximately 5 to 10 minutes). Add 300 milliliters of methanol and shake mechanically for 30 minutes. Dilute with methanol to volume and mix. Allow the excipients to settle. Quantitatively transfer and dilute a convenient aliquot of the supernatant with mobile phase (described in § 452.50(b)(1)(i)) to obtain a solution containing 125 micrograms of clarithromycin per milliliter (estimated). Filter through a suitable filter capable of removing particulate matter 0.5 micron in diameter.

(ii) *Calculations.* Calculate the clarithromycin content as follows:

$$\text{Milligrams of clarithromycin per tablet} = \frac{A_U \times P_s \times d}{A_s \times 1{,}000 \times n}$$

where:

A_U = Area of the clarithromycin peak (at a retention time equal to that observed for the clarithromycin standard) in the chromatogram of the sample;

A_S = Area of the clarithromycin peak in the chromatogram of the clarithromycin working standard;

P_S = Clarithromycin activity in the clarithromycin working standard solution in micrograms per milliliter;

d = Dilution factor of the sample; and

n = Number of tablets in the sample.

(2) *Loss on drying.* Proceed as directed in §436.200(c) of this chapter, using a sample weight of 1 to 2 grams.

(3) *Dissolution.* Proceed as directed in §436.215 of this chapter. The quantity Q (the amount of clarithromycin dissolved) is 80 percent at 30 minutes.

(4) *Identity.* Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention time for the peak of the active ingredient must be within 2 percent of the retention time for the peak of the corresponding reference standard.

[58 FR 26654, May 4, 1993]

§452.160 Azithromycin oral dosage forms.

§452.160a Azithromycin capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Azithromycin capsules are composed of azithromycin and one or more suitable and harmless diluents, disintegrants, lubricants, and wetting agents enclosed in a gelatin capsule. Each capsule contains azithromycin equivalent to 250 milligrams of azithromycin. The azithromycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of azithromycin that it is represented to contain. The moisture content of the capsules is not more than 5.0 percent. The capsules pass the dissolution test. The capsules pass the identity test. The azithromycin used conforms to the standards prescribed by §452.60(a)(1) of this part.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain;

(i) Results of tests and assays on:

(A) The azithromycin used in making the batch for potency, moisture, pH, residue on ignition, heavy metals, specific rotation, crystallinity, and identity.

(B) The batch for content, moisture, dissolution, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The azithromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 100 capsules.

(b) *Tests and methods of assay*—(1) *Azithromycin content.* Proceed as directed in §452.60(b)(1), preparing the sample solution and calculating the azithromycin content as follows:

(i) *Preparation of sample solution.* Quantitatively transfer the contents of one capsule into a 250-milliliter volumetric flask. Add about 175 milliliters of acetonitrile and shake on a reciprocating shaker for 30 minutes. Dilute to volume with acetonitrile, stopper the flask and mix well. Place 40 milliliters of the resulting suspension into a suitably sized centrifuge tube. Stopper the tube and centrifuge the suspension (about 10 minutes at 1,000 rpm). Pipet 2.0 milliliters of the supernatant into a 50-milliliter volumetric flask and dilute to volume with the mobile phase. Pipet 2.0 milliliters of this solution into a 25-milliliter volumetric flask and dilute to volume with mobile phase. The final dilution of the sample and standard must be identical. The final concentration of azithromycin in the sample solution is 0.003 milligram per milliliter (estimated).

(ii) *Calculations.* Calculate the azithromycin content as follows:

$$\text{Milligrams of azithromycin per capsule} = \frac{A_U \times P_S \times d}{A_S \times 1{,}000}$$

where:

A_U = Area of the azithromycin peak (at a retention time equal to that observed for the azithromycin standard) in the chromatogram of the sample;
A_S = Area of the azithromycin peak of the azithromycin working standard;
P_S = Azithromycin activity in the azithromycin working standard solution in micrograms per milliliter; and
d = Dilution factor of the sample = 250×50×25/2×2.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Dissolution test.* Proceed as directed in § 436.215 of this chapter. The quantity Q (the percentage of azithromycin activity dissolved) is 75 percent within 45 minutes.

(4) *Identity.* Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section the retention time for the peak of the active ingredient must be with 2 percent of the retention time for the peak of the corresponding reference standard.

[58 FR 26658, May 4, 1993. Redesignated at 59 FR 52078, Oct. 14, 1994.]

§ 452.160b Azithromycin for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Azithromycin for oral suspension is a dry mixture of azithromycin with a suitable and harmless buffer substance, sweetener, diluent, anticaking agent, and flavorings. The dry mixture is packaged in single dose packets each containing 1,000 milligrams of azithromycin. The azithromycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of azithromycin that it is represented to contain. Its moisture content is not more than 1.5 percent. When constituted as directed in the labeling, the pH of the suspension is not less than 9 and not more than 11. It gives a positive identity test for azithromycin. The azithromycin used conforms to the standards prescribed by § 452.60(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain;

(i) Results of tests and assays on:

(A) The azithromycin used in making the batch for potency, moisture, pH, residue on ignition, heavy metals, specific rotation, crystallinity, and identity.

(B) The batch for content, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The azithromycin used in making the batch: 10 packages, each containing approximately 1,000 milligrams.

(B) The batch: A minimum of 30 packages.

(b) *Tests and methods of assay*—(1) *Azithromycin content.* Proceed as directed in § 452.60(b)(1), preparing the dissolving solvent and sample solution and calculating the azithromycin content as follows:

(i) *Dissolving solvent.* Dissolve 2.2 grams of potassium phosphate monobasic in 1,590 milliliters of ultrapure deionized or high-performance liquid chromatographic-grade water. Add 600 milliliters of 2-propanol, 480 milliliters of ethanol, and 330 milliliters of acetonitrile, adjust to pH 8.4 with 10*M* potassium hydroxide and shake on a reciprocating shaker for 30 minutes. The dissolving solvent is 0.01*M* monobasic potassium phosphate:2-propanol:ethanol:acetonitrile (53:20:16:11, by volume).

(ii) *Preparation of sample solution.* Quantitatively transfer the contents of one package into a 500-milliliter volumetric flask. Add about 350 milliliters of dissolving solvent and shake on a reciprocating shaker for 30 minutes. Dilute to volume with dissolving solvent, stopper the flask, and mix well. Place 40 milliliters of the resulting suspension into a suitably sized centrifuge tube. Stopper the tube and centrifuge the suspension (about 20 minutes at 1,000 revolutions per minute). Pipet 10.0 milliliters of the diluted solution into a 50-milliliter volumetric flask and dilute to volume with mobile phase (described in § 452.60(b)(1)(i)). Pipet 2.0 milliliters of the diluted solution into a 50-milliliter volumetric flask and dilute to volume with mobile phase. The final dilution of the sample and standard

must be identical. The final concentration of azithromycin in the sample solution is 0.003 milligram per milliliter (estimated).

(iii) *Calculations.* Calculate the azithromycin content as follows:

$$\text{Milligrams of azithromycin per package} = \frac{A_U \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_U = Area of the azithromycin peak in the chromatogram of the sample (at a retention time equal to that observed for the azithromycin standard);

A_S = Area of the azithromycin peak in the chromatogram of the azithromycin working standard;

P_S = Azithromycin activity in the azithromycin working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample = 500 X 50/10 X 50/10 X 50/2.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug constituted as directed in the labeling. Allow the constituted suspension to sit for 10 minutes undisturbed before making the measurement.

(4) *Identity.* Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention time for the peak of the active ingredient must be within 2 percent of the retention time for the peak of the corresponding reference standard.

[59 FR 52078, Oct. 14, 1994]

§452.175 Troleandomycin oral dosage forms.

§452.175a Troleandomycin capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Troleandomycin capsules are capsules composed of troleandomycin and one or more suitable buffers, diluents, binders, lubricants, and colorings. Each capsule contains 125 milligrams or 250 milligrams of troleandomycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of troleandomycin that it is represented to contain. The loss on drying is not more than 5 percent. The troleandomycin used conforms to the standards prescribed by §452.75(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The troleandomycin used in making the batch for potency, loss on drying, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The troleandomycin used in making the batch: 10 packages, nine containing approximately equal portions of not less than 500 milligrams and one containing not less than 2 grams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.106 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing sufficient 80 percent isopropyl alcohol solution (solution 15) to obtain a stock solution containing 1,000 micrograms of troleandomycin per milliliter (estimated). Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 25 micrograms of troleandomycin per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 48 FR 3960, Jan. 28, 1983; 50 FR 19921, May 13, 1985]

§452.175b Troleandomycin oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Troleandomycin oral suspension is troleandomycin and one or more suitable buffers, dispersants, flavorings, colorings, and preservatives suspended in a suitable and harmless

vehicle. Each milliliter contains 25 milligrams of troleandomycin. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of troleandomycin that it is represented to contain. Its pH is not less than 5.0 and not more than 8.0. The troleandomycin used conforms to the standards prescribed by § 452.75(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The troleandomycin used in making the batch for potency, loss on drying, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The troleandomycin used in making the batch: 10 packages, nine containing approximately equal portions of not less than 500 milligrams and one containing not less than 2 grams.

(*b*) The batch: A minimum of five immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dilute an accurately measured representative portion of the sample with 80 percent isopropyl alcohol solution (solution 15) to obtain a stock solution containing 1,000 micrograms of troleandomycin per milliliter (estimated). Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 25 micrograms of troleandomycin per milliliter (estimated).

(2) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted sample.

[39 FR 19149, May 30, 1974, as amended at 48 FR 3960, Jan. 28, 1983; 50 FR 19921, May 13, 1985]

§ 452.175c Troleandomycin for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Troleandomycin for oral suspension is troleandomycin with suitable buffers, dispersants, preservatives, colorings, and flavorings. When the suspension is prepared as directed in its labeling, each milliliter contains 25 milligrams of troleandomycin. However, if it is for pediatric use, each milliliter contains 100 milligrams of troleandomycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of troleandomycin that it is represented to contain. Its loss on drying is not more than 2 percent. The pH of the suspension, when prepared as directed in its labeling, is not less than 5.0 and not more than 7.0. The troleandomycin used conforms to the standards prescribed by § 452.75(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The troleandomycin used in making the batch for potency, loss on drying, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency, loss on drying, and pH.

(ii) Samples required:

(*a*) The troleandomycin used in making the batch: 10 packages, nine containing approximately equal portions of not less than 500 milligrams and one containing not less than 2 grams.

(*b*) The batch: A minimum of five immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Reconstitute the drug as directed in the labeling. Dilute an accurately measured representative portion of the sample with sufficient 80 percent isopropyl alcohol solution (solution 15) to obtain a stock solution

containing 1,000 micrograms of troleandomycin per milliliter (estimated). Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 25 micrograms of troleandomycin per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension obtained after reconstituting the drug as directed in its labeling.

[39 FR 19149, May 30, 1974, as amended at 48 FR 3960, Jan. 28, 1983; 50 FR 19921, May 13, 1985]

§ 452.175d Troleandomycin chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Each troleandomycin chewable tablet contains an amount equivalent to 125 milligrams of troleandomycin with suitable diluents, binders, buffers, colorings, and flavorings. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of troleandomycin that it is represented to contain. The loss on drying is not more than 5 percent. The troleandomycin used conforms to the standards prescribed by § 452.75(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The troleandomycin used in making the batch for potency, loss on drying, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The troleandomycin used in making the batch: 10 packages, nine containing approximately 500 milligrams each and one containing approximately 2 grams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 80 percent isopropyl alcohol solution (solution 15) to obtain a stock solution containing 1,000 micrograms of troleandomycin per milliliter (estimated). Blend 3 to 5 minutes. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 25 micrograms of troleandomycin per milliliter (estimated).

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 48 FR 3960, Jan. 28, 1983; 48 FR 36571, Aug. 12, 1983; 50 FR 19921, May 13, 1985]

Subpart C—Injectable Dosage Forms

§ 452.225 Erythromycin ethylsuccinate injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ethylsuccinate injection is erythromycin ethylsuccinate and butylaminobenzoate dissolved in polyethylene glycol 400. It contains a suitable and harmless preservative. Each milliliter contains 50 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain. It contains 2 percent butylaminobenzoate. It is sterile. Its moisture content is not more than 1.5 percent. The erythromycin ethylsuccinate used conforms to the standards prescribed therefore by § 452.25a(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, each immediate container shall bear on its label and labeling the statement: ''Warning—For intramuscular use only''.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin ethylsuccinate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency, sterility, and moisture.

(ii) Samples required:

(*a*) The erythromycin ethylsuccinate used in making the batch: 10 packages, each containing 500 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation, except that if the product is sterilized after filling, a representative sample consisting of 10 immediate containers from each sterilizer load. If only one sterilizer load is involved, the sample shall consist of 20 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: By means of a suitable hypodermic needle and syringe, remove an accurately measured representative volume of the sample and dilute with sufficient methyl alcohol to give a solution containing 1.0 milligram of erythromycin base per milliliter (estimated). Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except use a bacterial-retentive membrane resistant to the solvent polyethylene glycol 400 and add 1 milliliter from each immediate container directly to the membrane, thus eliminating the preliminary solubilization step.

(3) [Reserved]

(4) *Moisture.* Proceed as directed in §436.201(e)(1) of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, 19921, May 13, 1985]

§452.230 Sterile erythromycin gluceptate.

The requirements for certification and the tests and methods of assay for sterile erythromycin gluceptate packaged for dispensing are described in §452.30a.

[46 FR 16685, Mar. 13, 1981]

§452.232 Erythromycin lactobionate injectable dosage forms.

§452.232a Erythromycin lactobionate for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin lactobionate for injection is a dry mixture of erythromycin lactobionate and a suitable preservative. It contains the equivalent of 300 milligrams, 500 milligrams, or 1 gram of erythromycin per vial. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 5 percent. Its pH is not less than 6.5 and not more than 7.5. The erythromycin used conforms to the standards prescribed by §452.10(a)(1) (i), (iii), (iv), (v), (vi), (vii), and (viii).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, pH, moisture, residue on ignition, heavy metals, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 containers, each consisting of not less than 500 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 12 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove the total withdrawable contents from

each container represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the preparation, withdraw an accurately measured volume from each container. Dilute with sterile distilled water to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 30 milligrams of erythromycin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using a concentration of 50 milligrams of erythromycin per milliliter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, 19921, May 13, 1985. Redesignated at 51 FR 35216, Oct. 2, 1986]

§ 452.232b Sterile erythromycin lactobionate.

The requirements for certification and the tests and methods of assay for sterile erythromycin lactobionate packaged for dispensing are described in § 452.32a.

[51 FR 35216, Oct. 2, 1986]

Subpart D—Ophthalmic Dosage Forms

§ 452.310 Erythromycin ophthalmic ointment.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ophthalmic ointment is erythromycin in a suitable and harmless ointment base. Each gram of ointment contains 5 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain. It is sterile. The moisture content is not more than 1 percent. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1) (i), (iii), (iv), (v), (vii), and (viii).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, pH, moisture, residue on ignition, crystallinity, and identity.

(*b*) The batch for potency, sterility, and moisture.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing 500 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of five immediate containers.

(*2*) For sterility testing: Twenty immediate containers, collected at regular intervals throughout each filling operation.

(b)(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place an accurately weighed representative portion of the ointment in a separatory funnel containing 50 milliliters of reagent-grade petroleum ether. Shake until dissolved. Wash with four separate washings of a 4:1 mixture of methyl alcohol and distilled water. Combine the washings and bring to volume with the methyl alcohol-water solution in a volumetric flask. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(3) of that section.

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 19149, May 30, 1974, as amended at 49 FR 5097, Feb. 10, 1984; 50 FR 19921, May 13, 1985]

Subpart E—[Reserved]

Subpart F—Dermatologic Dosage Forms

§ 452.510 Erythromycin dermatologic dosage forms.

§ 452.510a Erythromycin ointment.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin ointment is erythromycin in a suitable and harmless ointment base. It may contain suitable preservatives. Each gram of ointment contains 20 milligrams of erythromycin. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of erythromycin that it is represented to contain. The moisture content is not more than 1.0 percent. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1) (i), (iii), (iv), (v), (vii), and (viii).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, pH, moisture, residue on ignition, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing not less than 500 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place an accurately weighed representative portion of the ointment in a separatory funnel containing 50 milliliters of reagent-grade petroleum ether. Shake until dissolved. Wash with four separate washings of a 4:1 mixture of methyl alcohol and distilled water. Combine the washings and bring to volume with the methyl alcohol-water solution in a volumetric flask. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 19149, May 30, 1974, as amended at 49 FR 5097, Feb. 10, 1984; 49 FR 47829, Dec. 7, 1984; 50 FR 47214, Nov. 15, 1985]

§ 452.510b Erythromycin topical solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin topical solution contains in each milliliter 15.0 or 20.0 milligrams of erythromycin. It may also contain one or more suitable and harmless solvents, surfactants, buffer substances, diluents, and perfumes. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of erythromycin that it is represented to contain. If it contains 15.0 milligrams of erythromycin per milliliter, its moisture content is not more than 5.0 percent. If it contains 20.0 milligrams of erythromycin per milliliter, its moisture content is not more than 8.0 percent, except if it contains acetone, its moisture content is not more than 2.0 percent. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1), except heavy metals.

(2) *Packaging.* In addition to the requirements of § 432.1 of this chapter, it may either be dispensed on individually packaged pledgets, each individual pledget containing 0.8 milliliter of erythromycin topical solution, or in a jar containing 60 pledgets. The jar contains 0.8 milliliter of erythromycin topical solution per pledget. Although the pledgets in the jar are not individually packaged, the drug is uniformly distributed throughout the pledgets. The erythromycin topical solution used on the pledgets contains 20 milligrams of erythromycin per milliliter.

(3) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(4) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay.* If the erythromycin topical solution is dispensed on a pledget, express the contents of a representative number of pledgets into a suitable container to obtain a volume of sample adequate to perform each assay described in paragraph (b)(1) and (2) of this section.

(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion of the sample and dilute with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in §436.201 of this chapter, except if the sample contains acetone, in lieu of Solvent A, use a mixture of pyridine and methanol (1:1).

[46 FR 2995, Jan. 13, 1981, as amended at 48 FR 51293, Nov. 8, 1983; 49 FR 374, Jan. 4, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 19921, May 13, 1985; 50 FR 20204, May 15, 1985; 54 FR 47352, Nov. 14, 1989; 54 FR 50472, Dec. 6, 1989]

§452.510d Erythromycin-benzoyl peroxide topical gel.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin-benzoyl peroxide topical gel is erythromycin packaged in combination with a suitable and harmless gel containing benzoyl peroxide and one or more suitable dispersants, stabilizing agents, perfumes, and wetting agents. When reconstituted as directed in the labeling, each gram contains 30 milligrams of erythromycin and 50 milligrams of benzoyl peroxide. The erythromycin content is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of erythromycin that it is represented to contain. The benzoyl peroxide content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the milligrams of benzoyl peroxide that it is represented to contain. The erythromycin used conforms to the standards prescribed by §452.10(a)(1), except with respect to heavy metals.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for erythromycin content and benzoyl peroxide content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) The erythromycin used in making the batch: 5 packages, each containing approximately 100 milligrams.

(*b*) The batch: A minimum of 8 containers.

(b) *Tests and methods of assay*—(1) *Erythromycin content.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Place an accurately weighed representative portion of the constituted product into a high-speed glass blender jar containing 0.5 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with

solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Benzoyl peroxide content.* Reconstitute the sample as directed in the labeling. Place an accurately weighted representative portion (about 2.5 grams) of the constituted product into a tared 250-milliliter glass-stoppered flask. Add 50 milliliters of glacial acetic acid and 20 milliliters of methylene chloride. Stopper and shake vigorously to disperse the gel. Add 1.0 milliliter phenylsulfide, swirl, stopper, and allow to stand at room temperature for 2 minutes. Purge the flask with nitrogen for 3 seconds. Add 5 milliliters for freshly prepared saturated sodium iodide solution, stopper, and swirl to mix. Let stand in the dark for 30 minutes. Add 50 milliliters of previously boiled and cooled distilled water and titrate the liberated iodine with 0.1*N* sodium thiosulfate, adding starch T.S. near the endpoint. Perform a blank determination and correct the sample titer. Each milliliter of 0.1*N* sodium thiosulfate is equivalent to 12.11 milligrams of benzoyl peroxide. Calculate the benzoyl peroxide content as follows:

$$\text{Percent benzoyl peroxide} = \frac{V_u \times \text{Normality of sodium thiosulfate} \times 12.11}{\text{Sample weight in grams}}$$

where:

V_u=Milliliters of sodium thiosulfate used in the titration of the sample minus the milliliters of sodium thiosulfate used in the titration of the sample blank.

[49 FR 47485, Dec. 5, 1984; 49 FR 49090, Dec. 18, 1984; 49 FR 49449, Dec. 20, 1984, as amended at 55 FR 11584, Mar. 29, 1990]

§ 452.510e Erythromycin topical gel.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin topical gel is erythromycin in a suitable and harmless gel. Each gram contains 20 milligrams of erythromycin. The erythromycin content is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of erythromycin that it is represented to contain. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1), except with respect to heavy metals.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each request shall contain:

(i) Results of tests and assays on:

(A) The erythromycin used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(B) The batch for erythromycin content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The erythromycin used in making the batch: 5 packages, each containing approximately 100 milligrams.

(B) The batch: A minimum of 8 containers.

(b) *Tests and methods of assay; erythromycin content.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place approximately 1 gram, accurately weighed, of the product into a high-speed glass blender jar containing 200 milliliters of 0.5 percent (volume by volume) polysorbate 80 in 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

[53 FR 12415, Apr. 14, 1988; 53 FR 16837, May 11, 1988]

Subpart G—[Reserved]

Subpart H—Rectal Dosage Forms

§ 452.710 Erythromycin suppositories.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin suppositories contain in each suppository 125 milligrams of erythromycin in a suitable and harmless base. The erythromycin content is satisfactory if it is not less than 90 percent nor more than 120 percent of the number of milligrams of

erythromycin that it is represented to contain. The moisture content is not more than 1.0 percent. The erythromycin used conforms to the standards prescribed by § 452.10(a)(1), (i), (iii), (iv), (v), (vii), and (viii), except its moisture content is not more than 5.0 percent.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The erythromycin used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The erythromycin used in making the batch: 10 packages, each containing not less than 500 milligrams.

(*b*) The batch: A minimum of 30 suppositories.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of suppositories for 3 to 5 minutes in a high-speed glass blender with 200 milliliters of methyl alcohol. Add 300 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), and blend again for 3 to 5 minutes. Remove an aliquot and dilute with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 19149, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

Subpart I—[Reserved]

Subpart J—Certain Other Dosage Forms

§ 452.910 Erythromycin for prescription compounding.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Erythromycin for prescription compounding is the odorless, white to grayish-white or slightly yellow compound of a kind of erythromycin or a mixture of two or more such compounds. It is so purified and dried that:

(i) It contains not less than 850 micrograms of erythromycin per milligram calculated on an anhydrous basis.

(ii) Its moisture content is not more than 10 percent.

(iii) Its pH is not less than 8.0 nor more than 10.5.

(iv) Its residue on ignition is not more than 2.0 percent.

(v) It gives a positive identity test for erythromycin.

(vi) It is crystalline.

(2) *Packaging.* The immediate container shall be a tight container as defined by the United States Pharmacopeia XXI. It shall be so sealed that the contents cannot be used without destroying such seal. Each such container shall contain 10 grams, 25 grams, or 100 grams of erythromycin.

(3) *Labeling.* In addition to the requirements of § 432.5(a)(3) of this chapter, each package shall bear on its outside wrapper or container and on the immediate container the following:

(i) The statement ''Caution: Federal law prohibits dispensing without prescription.''

(ii) The statement ''Not sterile.''

(iii) The batch mark.

(iv) The number of micrograms of erythromycin activity in each milligram of erythromycin and the number of grams of erythromycin in the immediate container.

(v) The statement ''The potency of this drug cannot be assured for longer than 90 days after the container is first opened for compounding a prescription.''

(vi) The statements ''For use only in extemporaneous prescription compounding. Not for manufacturing use.''

(4) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and

Research: 10 packages, each containing not less than 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Dilute this solution further with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to obtain a stock solution containing 1.0 milligram of erythromycin base per milliliter (estimated). Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(2) *Moisture*. Proceed as directed in §436.201 of this chapter.

(3) *pH*. Proceed as directed in §436.202 of this chapter, except standardize the pH meter with pH 7.0 and pH 10.0 buffers and prepare the sample as follows: Dissolve 200 milligrams of sample in 5 milliliters of reagent grade methyl alcohol. Add 95 milliliters of water and mix. Record the pH when an equilibrium value has been reached.

(4) *Residue on ignition*. Proceed as directed in §436.207(a) of this chapter.

(5) *Identity test*. Proceed as directed in §436.211 of this chapter, using the sample preparation method described in paragraph (b)(3) of that section.

(6) *Crystallinity*. Proceed as directed in §436.203(a) of this chapter.

[51 FR 35213, Oct. 2, 1986, as amended at 55 FR 11584, Mar. 29, 1990; 55 FR 25392, June 21, 1990]

PART 453—LINCOMYCIN ANTIBIOTIC DRUGS

Subpart A—Bulk Drugs

Sec.

Subpart B—Oral Dosage Forms

Subpart C—Injectable Dosage Forms

Subparts D–E—[Reserved]

Subpart F—Dermatologic Dosage Forms

AUTHORITY: Sec. 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357).

Subpart A—Bulk Drugs

§453.20 Clindamycin hydrochloride hydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Clindamycin hydrochloride hydrate is the hydrated hydrochloride salt of clindamycin. It is so purified and dried that:

(i) Its clindamycin content is not less than 800 micrograms of clindamycin per milligram.

(ii) Its microbiological activity is not less than 800 micrograms of clindamycin per milligram.

(iii) [Reserved]

(iv) Its moisture content is not less than 3.0 percent and not more than 6.0 percent.

(v) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 3.0 and not more than 5.5.

(vi) It is crystalline.

(vii) It passes the identity test for clindamycin hydrochloride hydrate.